REMARKS

The present invention is directed to solid states of pantoprazole. Claims 1-5, 13-18, and 41-45 are pending. In an Office Action dated April 18, 2005, the Office rejected claims 1-5, 13-18, and 41-45. Claims 41 and 45 have been amended to recite the crystalline solid pantoprazole of claim 1 or 13. This amendment is supported by claims 41 and 45 as originally filed and the specification at paragraph [0028].

Claims 3, 5, 15, and 17 have been amended to include the figures to which they refer. Support for this amendment can be found in the specification at paragraphs [0019] and [0022].

Claim 23 was never presented in the original application, which presented claims 1-22 and 24-50. The election requirement mailed January 14, 2005, did not take notice of the incorrect enumeration and neither did the election requirement by applicants mailed on February 14, 2005. To avoid confusion and maintain the original claim enumeration, applicants now cancel claim 23.

35 U.S.C. § 102 Rejections

Claims 1-5, 13-18, and 41-45 were rejected under 35 U.S.C. § 102 (a), (b), and/or (e) as allegedly being anticipated by US 2003/0036554 to Avrutov et al. ("Avrutov"), US 6,723,852 to Maimo ("Maimo"), US 4,758,579 to Kohl et al. ("Kohl 1"), and Kohl, et al., *J. Med. Chem.*, 1992, 35, pp. 1049-1057 ("Kohl 2"). Applicants respectfully traverse this rejection.

Avrutov cannot form the basis for a 35 U.S.C. § 102(a), (b), or (e) rejection. Avrutov is not prior art under 35 U.S.C. § 102(a) or (e) because Avrutov and the present application share inventive entity. Avrutov is not prior art under 35 U.S.C. § 102(b) because it was not published more than one year before the priority date of the present application. The present application was filed on March 12, 2003 and claims priority to U.S. Provisional Application No. 60/464,358, which was filed on April 22, 2003. Avrutov was published on February 20, 2003, less than one year before the earliest filing date.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference."

Verdegaal Bros., Inc. v. Union Oil Co. of California, 814 F.2d 628, 631 (Fed. Cir. 1987) (emphasis added). *See also* MPEP § 2131.

Each of claims 1-5, 13-18, and 41-45 encompasses "crystalline solid pantoprazole" having a particular powder x-ray diffraction pattern (PXRD) or a pharmaceutical composition thereof.

Maimo discloses a method for the preparation of pantoprazole in solid form. *See* Maimo, Example 18, col. 9, ll. 38-53. Maimo does not, however, disclose a powder x-ray diffraction pattern for the pantoprazole prepared. A powder x-ray diffraction pattern is an element of each of claims 1-5, 13-18, and 41-45. Since Maimo does not disclose that element, it cannot anticipate claims 1-5, 13-18, and 41-45.

Kohl 1 discloses a genus of compounds, which encompasses pantoprazole. *See* Kohl 1, col. 2, ll. 1-33. Kohl 1 also discloses the species pantoprazole. *See* Kohl 1, col. 5, ll. 23-24; col. 35, ll. 10-13. Kohl 1 does not disclose a powder x-ray diffraction pattern for pantoprazole. Since a powder x-ray diffraction pattern is an element of each of claims 1-5, 13-18, and 41-45, Kohl 1 cannot anticipate claims 1-5, 13-18, and 41-45.

Kohl 2 discloses a method for the preparation of pantoprazole in solid form. *See* Kohl 2, p. 1054, right column. Kohl 2 discloses nuclear magnetic resonance spectroscopy data for the pantoprazole prepared. *Id.* Kohl 2 does not disclose a powder x-ray diffraction pattern for the pantoprazole prepared. Since a powder x-ray diffraction pattern is an element of each of claims 1-5, 13-18, and 41-45, Kohl 2 cannot anticipate claims 1-5, 13-18, and 41-45.

In light of the foregoing arguments, the rejection of claims 1-5, 13-18, and 41-45 under 35 U.S.C. § 102(a), (b) and (e) cannot stand and should be withdrawn.

35 U.S.C. § 103 Rejections

Claims 1-5, 13-18, and 41-45 were rejected under 35 U.S.C. § 103(a) as allegedly being obvious over the teachings of Avrutov, Maimo, Kohl 1, and Kohl 2, in view of general reference materials Haleblian, et al., *J. Pharm. Sci.*, 1969, 58, pp. 911-929 ("Haleblian"), Muzaffar, et al., *J. Pharmacy*, 1979, 1(1), pp. 59-66 ("Muzaffar"), Rouhi, Chem. & Eng'g News, Feb. 2003, pp. 32-35 ("Rouhi"), U.S.

Pharmacopeia, 1995, pp. 1843-1844 ("USP 1995"), and Concise Encyclopedia of Chem., 1993, pp. 872-873 ("Encyclopedia"). Applicants respectfully traverse.

As discussed above, Avrutov is not prior art under 35 U.S.C. § 102. Therefore, the Office cannot rely upon Avrutov as a basis of rejection under 35 U.S.C. § 103. *See* MPEP § 2141.01(I).

The Federal Circuit in *In re Dembiczak*, 175 F.3d 994 (Fed. Cir. 1999), set forth three requirements to make out a *prima facie* case of obviousness under 35 U.S.C. § 103(a) in light of the prior art. In order to be *prima facie* obvious: (i) there must be some teaching or suggestion in the prior art to modify or combine references to form the claimed invention, (ii) there must be a reasonable expectation of success taught or suggested in the prior art, and (iii) all of the elements of the claimed invention must be found in the prior art. *See also* M.P.E.P. § 2143. In order to meet its burden to show that the claims are *prima facie* obvious in light of the prior art, the Office must expressly point to something in the references themselves, something in the nature of the problem to be solved, or something in the general knowledge of persons reasonably skilled in the art that would constitute objective evidence of a teaching or suggestion to combine the cited references. *See In re Lee*, 277 F.3d 1338 (Fed. Cir. 2002).

The Office Action cites Maimo, Kohl I, and Kohl II as "teach[ing] the crystal forms of the instant known compound." Office Action, p. 4. As discussed above, Maimo, Kohl 1, and Kohl 2 disclose pantoprazole. *See* Maimo, Example 18, col. 9, ll. 38-53; Kohl 1, col. 5, ll. 23-24; col. 35, ll. 10-13; Kohl 2, p. 1054, right column. However, none of Maimo, Kohl 1, or Kohl 2 discloses any data to teach or suggest that the pantoprazole is in crystalline form or could be obtained in crystalline form. Furthermore, none of the cited references teach the PXRD pattern recited in the claims.

The Office Action cites Haleblian and Muzaffar as teaching that "compounds exist as polymorphs". Haleblian discusses polymorphism in general, examines the behavior of polymorphs in pharmaceutical dosage forms, and discusses methods used to study polymorphism. *See* Haleblian, pp. 911-929. Muzaffar discusses polymorphism and examines whether polymorphic forms of compounds exhibit different pharmaceutical properties than amorphous forms of those compounds. *See* Muzaffar, pp. 59-66. The references merely generically discuss polymorphs, and

neither Haleblian nor Muzaffar discloses pantoprazole or suggests that pantoprazole exhibits polymorphism.

The Office Action cites Rouhi, USP 1995, and Encyclopedia for the generic teaching that "at any particular temperature and pressure, only one crystalline form is thermodynamically stable." Rouhi discusses polymorphism and states that polymorphs tend to convert from less thermodynamically stable to more thermodynamically stable forms. *See* Rouhi, p. 32. USP 1995 discloses that many pharmaceutical compounds have been found to exhibit polymorphism, and that each polymorphic form is characterized by a unique powder x-ray diffraction pattern. *See* USP 1995, p. 1843, right column. Encyclopedia defines polymorphism in general and states that only one polymorphic form is stable at a given temperature and pressure. *See* Encyclopedia, pp. 872-873. None of Rouhi, USP 1995, or Encyclopedia disclose pantoprazole, suggest that pantoprazole exhibits polymorphism, nor suggest the particular PXRD of the claims.

When one skilled in the art views Maimo, Kohl 1, and Kohl 2, which disclose pantoprazole, in view of Haleblian, Muzaffar, Rouhi, USP 1995, and Encyclopedia, which discuss aspects of polymorphism in general, he is not lead to make the claimed polymorphic forms of pantoprazole. None of Haleblian, Muzaffar, Rouhi, USP 1995, or Encyclopedia teaches or suggests that pantoprazole exhibits polymorphism. To the contrary, Rouhi teaches that polymorphism is an unpredictable art. Rouhi notes that "no method yet exists to predict the polymorphs of a solid compound with significant certainty...[i]t is still not possible to figure out how many different ways a molecule can lie down with itself in a lattice." Rouhi, p. 32.

Polymorphism and polymorph generation are considered to be unpredictable by those skilled in the art. "[T]he possibility of polymorphism may exist for any particular compound, but the conditions required to prepare as yet unknown polymorphs are by no means obvious." Joel Bernstein, *Polymorphism in Molecular Crystals* 9 (Clarendon Press 2002). "No rules exist that allow prediction of whether a compound will exhibit polymorphism;" Byrn, S.R. *Solid-State Chemistry of Drugs* p. 7 (Academic Press 1982). "Until that time [that computer programs are able to predict stable crystal forms] the development scientist is handicapped in attempting to predict how many solid forms of a drug are likely to be found. Brittian, H.G., *Polymorphism in Pharmaceutical Solids* p. 185 (Marcel Dekker 1999). The Office

Action acknowledges the unpredictability of polymorphs: "No method exists to predict the polymorphs of a solid compound with any significant certainty." Office Action, p. 7. Accordingly, the claimed polymorphs could not be predicted merely from the disclosure of solid pantoprazole. At most the Office Action suggests that it might be obvious to try to find polymorphs of pantoprazole, but obvious to try is not the legal standard for establishing a *prima facie* case of obviousness. *See, e.g., In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988).

Because none of the cited references teaches or suggests the claimed crystalline forms, the rejection of claims 1-5, 13-18, and 41-45 under 35 U.S.C. § 103(a) cannot stand and should be withdrawn.

35 U.S.C. § 112 Rejections

Claims 1-5, 13-18, and 41-45 were rejected under 35 U.S.C. § 112 as allegedly lacking written description and enablement. Claims 2-5, 14-18, and 42-45 were rejected under 35 U.S.C. § 112 as allegedly indefinite.

Enablement

Claims 1-5, 13-18, and 41-45 were rejected under 35 U.S.C. § 112, first paragraph as allegedly lacking enablement. Applicants respectfully traverse.

The enablement requirement of 35 U.S.C. § 112, first paragraph is fulfilled when the patent discloses enough information about the claimed invention to enable one skilled in the art to make and use it without undue experimentation. *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988); MPEP § 2164.01.

The Office Action argues that the application "lacks description as to whether the pharmaceutical carriers are able to maintain the compound in the polymorphic form or solvates claimed or if the compound is stable and stays in the polymorphic form" and as to "how the pharmaceutical composition can be prepared in order to maintain the particular compound of a particular form with the particular infrared spectra and X-ray diffraction being claimed." Office Action, pp. 4-5. The Office Action also argues that the application has "not described how the polymorph forms and compositions being claimed will be maintained and prevented from converting to other forms when used in inhibiting gastric acid secretion." Office Action, p. 6. These arguments relate to limitations that are not claimed. The present claims do not

recite any limitations with respect to the crystalline forms maintaining their structure for any particular length of time. The claims are directed to pharmaceutical compositions containing the pantoprazole crystalline forms described. If the pantoprazole crystalline form were to convert to a different form upon administration of the drug, it would fall outside the scope of Applicants' claims. Accordingly, arguments relating to such a limitation are irrelevant.

The application describes the preparation of the claimed polymorphic forms of pantoprazole in sufficient detail to allow one skilled in the art to make and use them without undue experimentation. *See* Examples 1-20 (providing specific reaction conditions for the "crystallization" procedure and the "slurry" procedure for making the claimed compounds). The application also describes the claimed pharmaceutical compositions containing polymorphic forms of pantoprazole in sufficient detail to allow one skilled in the art to make and use them without undue experimentation. *See* Specification, pp. 7-11. As such, the disclosures meet the legal standard for enablement set forth in *In re Wands*.

The Office Action also argues that "the specification fails to show that the instant polymorphs or compositions containing the polymorphs inhibit any gastric acid secretion" and, therefore, that the specification does not enable one skilled in the art to use the pharmaceutical compositions to treat patients. Office Action, p. 7. The Applicants, however, have presented a credible basis for the polymorphs' utility in inhibiting gastric acid secretion in the specification, for example, at paragraphs [0006], which sets forth the utility of pantoprazole, and [0010], which discloses the utility of new polymorphic forms.

MPEP § 2164.04 states that an enablement rejection is only proper if "there is a reason to doubt the objective truth of the statements contained [in the specification]." In *In re Marzocchi*, 439 F.2d 220, 224 (CCPA 1971), the court instructs:

> [I]t is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure. (emphasis in original).

In this case, the Patent Office has not provided evidence that refutes the Applicants' presumptively accurate statement that the claimed pharmaceutical compositions can be used to inhibit gastric acid secretion.

In light of the foregoing arguments, the rejection of claims 1-5, 13-18, and 41-45 under 35 U.S.C. § 112, second paragraph as lacking enablement cannot stand and should be withdrawn.

Written Description

Claims 1-5, 13-18, and 41-45 were rejected under 35 U.S.C. § 112, second paragraph as allegedly lacking written description. Applicants respectfully traverse.

The Office Action treats written description and enablement as a single basis for rejection. *See* Office Action, pp. 4-9. The written description requirement, however, is separate and distinct from the enablement requirement of 35 U.S.C. § 112. *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1560 (Fed. Cir. 1991); MPEP § 2163(I).

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail so that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. *See, e.g., Vas-Cath, Inc.*, 935 F.2d at 1563. As long as a person of ordinary skill in the art would have understood the inventor to have been in possession of the claimed invention at the time of filing, even if not every nuance of the claims is explicitly described in the specification, the written description requirement is met. *In re Alton*, 76 F.3d 1168, 37 U.S.P.Q.2d 1578 (Fed. Cir. 1996). "*Ipsis verbis* disclosure is not necessary to satisfy the written description requirement." *Fujikawa v. Wattanasin*, 93 F.3d 1559, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996).

The claimed invention is adequately described by the specification, *e.g.*, at paragraphs [0019], [0022], and [0028], as well as the claims as originally filed. One of skill in the art would recognize that, at the time of filing, the present inventors had possession of the claimed crystalline forms of pantoprazole and pharmaceutical compositions comprising the same. The crystalline forms are described by their PXRD peaks, which is the most accepted way of characterizing crystalline forms. *See* U.S. Pharmacopeia, vol. 28, 2005, pp. 2513-2514. The pharmaceutical compositions

can be made by conventional techniques, which need not be disclosed in detail. *See* MPEP § 2163(II)(A)(3)(a).

Accordingly, the rejection of claims 1-5, 13-18, and 41-45 under 35 U.S.C. § 112, second paragraph as lacking written description cannot stand and should be withdrawn.

Indefiniteness

Claims 2-5, 14-18, and 42-45 have been rejected under 35 U.S.C. § 112, second paragraph as allegedly failing to particularly point out and distinctly claim the invention. Applicants respectfully traverse.

Claims fulfill the definiteness requirement of 35 U.S.C. § 112, second paragraph when they clearly define the metes and bounds of the invention. A claim meets the legal standard for definiteness where those skilled in the art would understand what is claimed when the claim is read in light of (1) the disclosures of the application, (2) the prior art, and (3) the knowledge of one of ordinary skill in the pertinent art. *Orthokinetics, Inc. v. Safety Travel Chairs, Inc.*, 806 F.2d 1565 (Fed. Cir. 1986); MPEP § 2173.02.

The Office Action asserts that claims 2-5, 14-18, and 42-45 lack antecedent basis because the claims are drawn to the compounds of claim 1 or 13 or the composition of claim 41. But the compound, *i.e.*, "crystalline solid pantoprazole," is explicitly recited in claims 1 and 13. Likewise, the "composition" is explicitly recited in claim 41. Thus, the dependent claims have proper antecedent basis.

The Office Action also asserts that the term "substantially" in claims 3-5, 15, and 17 is indefinite. Applicants note that the term "substantially" is not recited in claim 4. As to claims 3, 5, 15, and 17, the MPEP and courts have approved the use of the term "substantially" in claims so long as one skilled in the art can discern its meaning. *See* MPEP 2173.05(b)(D), citing *In re Mattison*, 509 F.2d 563 (CCPA 1960) and *Andrew Corp. v. Gabriel Electronics*, 847 F.2d 819 (Fed. Cir. 1988).

The term "substantially" is used in the claims 3, 5, 15, and 17 with respect to particular powder x-ray diffraction ("PXRD") patterns and infrared ("IR") spectra. The term "substantially" refers to the slight experimental variation inherent in any PXRD or IR measurement. Those skilled in the art are aware that this experimental variation is about ± 0.01 degrees 2 theta for PXRD measurements and about ± 0.08-

0.10% for IR measurements. *See* U.S. Pharmacopeia, vol. 28, 2005, pp. 2514, 2693. Since one skilled in the art appreciates this experimental variation, one skilled in the art can discern the meaning of the term "substantially" as used in claims 3, 5, 15 and 17. Therefore, the term "substantially" is definite under 35 U.S.C. § 112, second paragraph.

The Office Action also rejects claims 3, 5, 15 and 17 as incomplete. The amendment of claims 3, 5, 15, and 17 to include the figures renders this rejection moot.

In view of these arguments and amendments, the rejections of claims 2-5, 13-18, 42-43, and 45 under 35 U.S.C. § 112 cannot stand and should be withdrawn.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants respectfully submit that the present application is now compliant and the claims are in condition for allowance. Early and favorable action by the Examiner is earnestly solicited. If any outstanding issues remain, the examiner is invited to telephone the undersigned at the telephone number indicated below to discuss the same. No fee is believed to be due for the submission of this response. Should any fees be required, please charge such fees to Kenyon & Kenyon, LLP Deposit Account No. 11-0600.

Respectfully Submitted,

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